Remarks on Claim Status and Amendments

Claims 1-24 are pending. Claims 12, 17, and 24 are amended according to the proposals of the examiner attached to paper no. 19. Claims 12 and 24 are amended to specify that the encoded polypeptide "stimulates islet cell neogenesis." This is supported at column 5, lines 60-62 and column 7, lines 45-46. Claim 17 is amended to recite that the complementary mRNA produced by the anti-sense construct "prevents translation of the native mammalian INGAP mRNA." This is supported at column 8, lines 45-56, as well as by the ordinary meaning of the term "anti-sense construct."[1]

Interview Summary

Examiner Carlson graciously discussed the rejection for double-patenting on the telephone on October 21, 2003. She maintained that overlapping subject matter was sufficient to trigger a double-patenting rejection. Agreement was not reached on that point. She suggested amending the claims to eliminate overlap or explain how the claims do not overlap. She provided suggested claims for eliminating overlap by using closed claim language (consisting of). Below applicants explain how the claims do not overlap and/or are not rendered obvious by the copending claims.

Examiner Robinson discussed the Office Action Summary in paper no. 19 on October 28, 2003. She indicated that item no. 12 was erroneously checked and that there is no defect in the oath or declaration.

---

[1] Nucleic acid that has a sequence exactly opposite to an mRNA molecule made by the body; binds to the mRNA molecule to prevent a protein from being made. See also: transcription www.ornl.gov/TechResources/Human_Genome/glossary/glossary.html

A piece of DNA that produces the mirror image, or antisense messenger RNA, that is exactly opposite in sequence to one that directs the cells to produce a specific protein. Since the antisense RNA binds tightly to its image, it prevents the protein from being made. ozans.4mg.com/glossary.htm

An oligonucleotide or analog thereof that is complementary to a segment of RNA or DNA and that binds to it and inhibits its normal function. [IUPAC Medicinal Chemistry] www.genomicglossaries.com/content/Pharmaceutical_biology_glossary.asp

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 12, 17, and 24 were rejected as lacking an adequate written description. On June 21, 2002, Examiner Carlson proposed language to overcome this rejection. The Office Action, paper no. 19, at page 5, lines 6-8 indicates that the rejection will be overcome by the amendment. The Examiner's proposal is adopted in the current amendment to claims 12, 17, and 24. It is respectfully submitted that this amendment puts claims 12, 17, and 24 in compliance with 35 U.S.C. § 112, first paragraph. Withdrawal of this rejection is therefore requested.

Rejection for Non-Statutory Double Patenting

Claims 1-24 are provisionally rejected as unpatentable over claims 1-49 of S.N. 09/659,379. This rejection is respectfully traversed.

Because the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. 103(a) rejection, the factual inquiries set forth in *Graham v. John Deere Co.,* 383 U.S. 1 (1966) also are employed when making an obvious-type double patenting analysis. Manual of Patent Examining Procedure (M.P.E.P.), 8th ed., § 804(II)(B)(1). Section 103(a) of 35 U.S.C. states:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Obviousness under 35 U.S.C. § 103(a) is a question of law based on several factual inquiries:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.

Graham v. John Deere Co., 383 U.S. 1, 17 (1966). The U.S. Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of obviousness based on the results of the factual inquiries under *Graham*. The *prima facie* case requires three showings:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

> combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P., 8th ed., § 2142.

Obviousness does not require absolute predictability. At least some degree of predictability, however, is required to make a *prima facie* case. M.P.E.P., 8th ed., § 2143.02. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (C.C.P.A. 1976).

The disclosures of the specification of a cited patent or application are not to be applied in framing a double patenting rejection. "[A] double patenting rejection must rely on a comparison with the claims in an issued or to be issued patent." M.P.E.P. § 804, III. Moreover, all of the claim limitations must be considered. "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson,* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Merely asserting that two sets of claims are obvious over each other is insufficient to make a *prima facie* case. "Any obviousness-type double patenting rejection should make clear: (A) The differences between the inventions defined by the conflicting claims -- a claim in the patent compared to a claim in the application; and (B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent." M.P.E.P., 8th ed., § 804 (II)(B)(1).

The Board of Patent Appeals and Interferences in *Ex parte Michno*, 38 U.S.P.Q.2d 1211 (1993) stated: "The notion that a pending claim to a generic invention is necessarily patentably indistinct, in the sense of double patenting of the obviousness type, from a narrower patented claim encompassed by the generic claim was scotched by *In re Braat*, 937 F.2d 589 at 594, 19 U.S.P.Q.2d 1289 at 1293 (Fed. Cir. 1991)." *Michno* at 1212. The Board held that "a mere genus-species or broad-narrow relationship between pending and patented claims is not a litmus test for resolving the question of double patenting." *Michno* at 1212.

Where a two-way obviousness determination is required, an obvious-type double patenting rejection is appropriate only where each analysis compels a conclusion that the invention defined in the claims in issue is an obvious variation of the invention defined in a

claim in the other application/patent. If either analysis does not compel a conclusion of obviousness, no double patenting rejection of the obvious-type is made. M.P.E.P., 8th Ed., § 804, (II)(B)(1)(b). The two-way test applies if (A) administrative delay on the part of the Office caused delay in prosecution of the earlier filed application; and (B) applicant could not have filed the conflicting claims in a single (*i.e.,* the earlier filed) application.

In the present application, the results of the factual inquiries under *Graham v. John Deere Co.* do not support a *prima facie* case that claims 1-49 of copending application are obvious over claims 1-24. First, the prior art does not provide a suggestion to modify the cited reference. Second, there would not have been a reasonable expectation of success. Third, the cited prior claims do not teach or suggest all the claim limitations.

1. **Two-way Test Should Be Applied**

Under the two-way test, only if each application is obvious over the other should a rejection for double patenting be made in either application. M.P.E.P., 8th ed., § 804, (II)(B)(1)(b). The two-way test applies if (A) administrative delay on the part of the Office caused delay in prosecution of the earlier filed application; and (B) applicant could not have filed the conflicting claims in a single (*i.e.,* the earlier filed) application.

A two-way test is appropriate in the present application. There was administrative delay in the prosecution of the subject application. The application underlying the subject application for reissue was filed September 9, 1996, claiming benefit of a February 22, 1995 priority date. The application underlying the co-pending application for reissue was filed August 12, 1997, claiming priority to an October 30, 1996 application. The later filed underlying application issued first. Applicant caused no delay in the underlying subject application. The relevant dates are tabulated below.

Serial No.	Priority Date	Filing Date	Issue Date
709,662	February 22, 1995	September 9, 1996	November 24, 1998
909,725	October 30, 1996	August 12, 1997	September 8, 1998

The earlier issuance of the later-filed application evidences the Patent and Trademark Office's administrative delay.

Moreover, applicants could not have filed the two sets of claims in the earlier filed application because applicants had not yet invented the second invention when the first application was filed. A declaration regarding the relative dates of invention is enclosed.

Because applicants fulfill the two prerequisites for application of the two-way test, it should be applied. When the two-way test is applied, if either of the two sets of claims is not obvious over the other then no rejection for double-patenting should be made in either application. M.P.E.P., 8th ed., § 804, (II)(B)(1)(b).

2. **Scope and content of the prior art**

The first factual inquiry under *Graham* is to determine the scope and content of the prior art. 383 U.S. at 17. The scope and content of the claims cited as "prior art" are described below.

The cited reference claims

Claims 1-49 of copending application 09/659,379 are cited as rendering the subject claims obvious. The claims of the copending application are directed to expression constructs that encode mature INGAP protein and that explicitly exclude the signal sequence of INGAP protein.

Claim 1 recites "a first nucleotide sequence encoding amino acid residues 27 to 175 as shown in SEQ ID NO: 6... wherein a second nucleotide sequence encoding a signal peptide is not present immediately 5' of said first nucleotide sequence." Thus, co-pending claim 1 excludes residues 1-26. Dependent claims 2-12, 16, 19, and 20 similarly have this exclusion.

Co-pending independent claim 13 and its dependents (claims 14-17) have the same exclusion as claim 1. Independent claim 15 and its dependent claim 18 have the same exclusion as claim 1. Independent claim 47 similarly recites a "first nucleotide sequence encoding mature human INGAP...wherein a second nucleotide sequence encoding a signal peptide according to SEQ ID NO: 5 is not present immediately 5' of said first nucleotide sequence."

Co-pending independent claim 21 recites primers that amplify "a coding sequence consisting of nucleotides 12 to 456 of SEQ ID NO: 4." According to the specification of the copending application at column 12, lines 65 and following, SEQ ID NO: 4 does not contain the signal sequence and 5' UTR.

Co-pending independent claims 23, 29, and 45, and their dependent claims 22, 24-28, 30-44, 46, and 48-49, share the same recitation as co-pending claim 21. Thus, none of these claims encompasses the full sequence of SEQ ID NO: 6, which is the sequence of the pre-protein of INGAP.

3. **Differences between the "prior art" and claims 1-24**

The second factual inquiry under *Graham* is to ascertain the differences between the prior art and the claims at issue. 383 U.S. at 17.

The claims at issue are claims 1-24 of the subject application. Each of the subject application's pending claims 1-8, 15-16, and 18-22 recites a nucleotide sequence encoding the pre-protein, *i.e.*, including residues 1-25 of SEQ ID NO: 2. The claims of the co-pending application exclude amino acid residues 1-26 of SEQ ID NO: 6 (*i.e.*, of the pre-protein).[2] Thus these two sets of claims differ in the nucleotides encoding the amino terminal 25 or 26 amino acids that constitute the signal sequence of INGAP; one set of claims requires this region and the other set excludes it.

The subject application contains claims to probes (claims 9-11) and anti-sense constructs (claim 17) but not to primers. The co-pending application has claims to primers (claims 21, 22, and 49) but not to probes or anti-sense constructs. The claims to primers in the co-pending application require that the amplified sequence consist of nucleotides 12 to 456 of SEQ ID NO: 4, *i.e.*, the signal sequence is excluded. The primers hybridize to the 5' and 3' ends, respectively, of the "nucleotide sequence encoding mature human INGAP."

4. **Level of skill in the art**

The third factual inquiry under *Graham v. John Deere Co.* is to resolve the level of skill in the pertinent art. 383 U.S. at 17. The person of ordinary skill is described in *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*:

> The person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art. The actual

[2] The number of amino acids in the signal sequence differ between the two applications due to the difference in the assignment of the first codon. The subject application discloses only a single methionine residue at the N-terminus of the pre-protein, whereas the copending application discloses two methionine residues at the N-terminus.

> inventor's skill is not determinative. Factors that may be considered in determining level of skill include: type of problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field. Not all such factors may be present in every case, and one or more of them may predominate.

807 F.2d 955,962-63, 1 U.S.P.Q.2d 1196, 1201 (Fed. Cir. 1986). The person of ordinary skill would have been aware of all pertinent prior art relating to expression of cloned genes in heterologous host cells. The person of ordinary skill would have been aware of prior art which shows that it was not predictable that removal of a signal sequence would lead to improved expression. The hypothetical person of ordinary skill would have been aware of Xu *et al.*, "The role of the leader sequence coding region in expression and assembly of bacteriorhodopsin," *J. Biol. Chem. 270:* 24858-24863, 1995, copy enclosed. Xu describes the deletion of a 13-amino acid signal sequence (leader sequence) in a rhodopsin protein. The deletion of the leader resulted in unstable mRNA and almost no rhodopsin protein production. See Abstract. Xu postulates that the loss of protein production is due to degradation of the mRNA.

The hypothetical person of ordinary skill would have been aware of Jarvis *et al.*, "Influence of different signal peptides and prosequences on expression and secretion of human tissue plasminogen activator in the baculovirus system," *J. Biol. Chem. 268:* 16754-16762, 1993, copy enclosed. Jarvis teaches that deletion of the native signal sequence of human t-PA (tissue plasminogen activator) failed to increase t-PA production in a heterologous system. Page 16759 and Figure 8. Replacement of the signal sequence with native signal sequences also did not increase t-PA production. Jarvis concludes that other factors are involved in preventing high level production. See Abstract.

The hypothetical person of ordinary skill would have been aware of Berges *et al.*, "Combined effects of the signal sequence and the major chaperone proteins on the export of human cytokines in *Escherichia coli,*" *App. and Env. Microbiol., 62:* 55-60, 1996, copy enclosed. Berges teaches that various combinations of signal peptides and proteins provide variable and unpredictable results. Some combinations are several-fold more efficiently translated than others. Some combinations lead to rapid growth arrest followed by slow cellular lysis. See page 49, discussion. These variations in expression among constructs employing the same signal sequence demonstrate that the identity and nature of the protein linked to the signal

sequence clearly influences heterologous expression efficiency in ways that are not predictable and do not depend solely on the presence or absence of a signal sequence.

Thus the hypothetical person of ordinary skill would have known that expression of cloned genes in heterologous host cells was unpredictable.

5. **Failure to establish a *prima facie* case of obviousness**

The U.S. Patent and Trademark Office bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103; only when a *prima facie* case has been established does the burden shift to the applicants to provide evidence or argument in rebuttal. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 U.S.P.Q.2d 1955, 1966 (Fed. Cir. 1993), *citing In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). In this case, the results of the factual inquiries carried out under *Graham* do not support a *prima facie* case that claims 1-49 of the copending application are obvious.

A *prima facie* case of obviousness requires a showing that the cited references themselves or the knowledge generally available to one of ordinary skill in the art contain a suggestion or motivation to modify the reference teachings. M.P.E.P. § 2142. The problem the 09/659,379 invention solves is obtaining expression of copious amounts of INGAP protein from a cloned INGAP gene in a heterologous host cell. The prior application (*i.e.*, the subject application) does not recognize the problem of poor expression of the cloned INGAP gene in a heterologous host cell. It thus does not teach or suggest any ways to overcome the problem. There is nothing in the subject application's claims that teaches or suggests that the nucleotide sequence encoding the signal sequence should be removed. There is nothing in the subject application's claims that indicates that removal of the coding sequence for the signal sequence would lead to improved expression levels.

Even if there were a suggestion or motivation to modify the teachings of the prior application's claims, those of skill in the art would not have had a reasonable expectation of success. An applicant may rebut a *prima facie* case of obviousness by providing sufficient evidence that demonstrates a substantial degree of unpredictability in a particular art area. *In re May,* 574 F.2d 1082, 1094, 197 U.S.P.Q. 601, 611 (C.C.P.A. 1978). The claims of the copending application are directed to constructs which explicitly exclude the coding sequence for

the signal sequence of INGAP. Unexpectedly, such constructs were found to solve the problem of very low expression found when using constructs containing the coding sequence for the signal sequence. Before the signalless constructs were made, a person of skill in the art could not have predicted that such constructs would improve the yield of INGAP protein produced.

Low yield in expressing mammalian proteins in heterologous systems can be caused by a multitude of factors. For example, the mammalian protein could be toxic to the host cell. The mammalian protein's mRNA could be unstable in the host cell, *e.g.*, due to absence of another mammalian binding protein. The mammalian protein could be insoluble in the host cell, *e.g.*, localizing to inclusion bodies. The mammalian protein could be inactivated by a host cell protein. The number of variables involved in expressing a heterologous protein in a host cell is large. These factors underscore the unpredictability in the field of heterologous protein expression.

As discussed above, the prior art indicates that there was indeed a great deal of unpredictability in expressing proteins in a heterologous host cell. Deletion of a signal sequence could be deleterious, leading to an unstable mRNA. See Xu, *supra.* Deletion of a signal sequence could fail to increase production of a protein in a heterologous system. See Jarvis, *supra.* The identity and nature of the protein affects the levels of expression in ways that were unpredictable at the time the invention was made. See Berges, *supra.* Thus, prior to the invention of the co-pending 09/659,379 application, it would not have been obvious that the removal of the signal sequence of INGAP would lead to increased production of INGAP in heterologous host cells.

Finally, the claims of the subject application do not suggest all the claim elements recited in the copending claims. Specifically, there is no suggestion to remove amino acids 1-25 in the subject application's claims. Thus the cited prior art does not suggest all of the claim elements in the 09/659,379 claims.

In rejecting claims 1-24 as obvious under the judicially-created doctrine of obviousness-type double patenting, the U.S. Patent and Trademark Office has failed to properly assess the scope and content of the prior art, the differences between the prior art and the claimed methods, and the level of skill in the art. A *prima facie* case of obviousness has therefore not been made. Even if a *prima facie* case had been presented, the demonstrated unpredictability in the art supports a conclusion of non-obviousness.

Because copending claims 1-49 would not have been obvious over subject claims 1-24, the two-way test for obviousness-type double patenting fails. If either set of claims is not obvious over the other, a double patenting rejection should not be maintained.

6. **Erroneous Factual Underpinnings to PTO's Obviousness Assertion**

The rejection appears to be based on a number of misapprehensions reflected in misstatements of fact in the Office Action. Applicants believe that correction of these misstatements should cause the Patent and Trademark Office to reconsider the propriety of the rejection.

First, the Patent and Trademark Office mischaracterizes the claimed subject matter in the co-pending application.

> Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the co-pending application are directed to a recombinant construct for expression of INGAP which comprises a nucleotide sequence that encodes the amino acids set forth in SEQ ID NO: 6.

Office Action (paper no. 19) at page 4, lines 12-15. None of the co-pending claims are directed to a nucleotide sequence encoding the amino acids set forth in SEQ ID NO: 6 *per se*. All of the co-pending claims specifically recite only a specific portion of these amino acids. Claim 1 recites "a first nucleotide sequence encoding amino acid residues 27 to 175 as shown in SEQ ID NO: 6... wherein a second nucleotide sequence encoding a signal peptide is not present immediately 5' of said first nucleotide sequence." Thus, co-pending claim 1 excludes residues 1-26. Dependent claims 2-12, 16, 19, and 20 similarly have this exclusion. Therefore, none of these claims are directed to a coding sequence for SEQ ID NO: 6.

Co-pending independent claim 13 and its dependents (claims 14-17) have the same exclusion as claim 1. Independent claim 15 and its dependent claim 18 have the same exclusion as claim 1. Independent claim 47 similarly recites a "first nucleotide sequence encoding mature human INGAP...wherein a second nucleotide sequence encoding a signal peptide according to SEQ ID NO: 5 is not present immediately 5' of said first nucleotide sequence."

Co-pending independent claim 21 recites primers that amplify "a coding sequence consisting of nucleotides 12 to 456 of SEQ ID NO: 4." According to the specification of the

copending application, SEQ ID NO: 4 does not contain the signal sequence and 5' UTR. See column 12, lines 65 and following. Thus, the subject matter of co-pending claim 21 and its dependent claims 22 and 49 do not encompass all of the amino acids set forth in SEQ ID NO: 6 as alleged by the Patent and Trademark Office.

Co-pending independent claims 23, 29, and 45, and their dependent claims 22, 24-28, 30-44, 46, and 48-49, share the same recitation as co-pending claim 21. Thus, none of these claims encompass the full sequence of SEQ ID NO: 6.

Second, the Patent and Trademark Office erroneously compares recited sequences in sequence listings rather than comparing properly construed claims.

> Note that the present application is directed to an isolated DNA molecule which encodes an INGAP protein set forth in SEQ ID NO: 2 and both sequences are identical with the exception of one residue (SEQ ID NO: 6 has an additional methionine in the beginning of the sequence.)

Office Action, paper no. 19, at page 4, lines 15-18. As detailed above, the claims of the co-pending application do not encompass SEQ ID NO: 6 *per se*. The claims are directed to a subsequence which specifically excludes the nucleotides encoding the signal sequence, *i.e.*, the first 26 amino acids.

The Office Action compares SEQ ID NO: 6 of the co-pending application to SEQ ID NO: 2 of the subject application and finds that they differ by only a single amino acid, a methionine. But this comparison of sequences in a sequence listing is not appropriate. A proper comparison should be made between the recited subject matter of the two sets of claims. "[A] double patenting rejection must rely on a comparison with the claims in an issued or to be issued patent." M.P.E.P. § 804 (III). Moreover, all of the claim limitations must be considered. *In re Wilson, supra.* If one compares the claimed subject matter, considering all of the recitations of the claims, one finds a much larger difference between the claims of the two applications. The claims of the co-pending application exclude amino acid residues 1-26 of SEQ ID NO: 6 (*i.e.*, of the pre-protein). Each of the subject application's pending claims 1-8, 15-16, and 18-22 recites a nucleotide sequence encoding the pre-protein, *i.e.*, including residues 1-25 of SEQ ID NO: 2. Thus the subject matter of the two sets of claims is far more distinct and non-overlapping than the single methionine residue that the Office Action acknowledged.

Third, the Patent and Trademark Office mischaracterizes the general subject matter of each application.

> Furthermore, the present application and co-pending application both claim probes, primers, and have claims directed to anti-sense strand which would render each other obvious.

Office Action, paper no. 19, sentence spanning pages 4 and 5. The subject application contains claims to probes (claims 9-11) and anti-sense constructs (claim 17), but not to primers. The co-pending application has claims to primers (claims 21, 22, and 49) but not to probes or anti-sense constructs.

	Probes	Anti-sense	Primers
Subject application, S.N. 09/717,095	+	+	-
Co-pending application, S.N. 09/659,379	-	-	+

Thus, these general subjects are not present in both applications as alleged by the Patent and Trademark Office. Thus, the subject matter of the two sets of claims does not overlap in the manner and to the extent described by the Patent and Trademark Office.

Conclusion

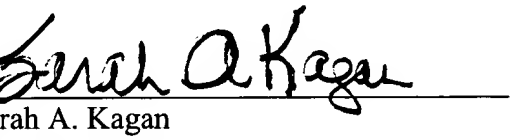
The Patent and Trademark Office has repeatedly asserted that "although the claims in the two applications are not identical, the claimed subject matter in both applications are an obvious variation of each other." See, *e.g.*, Paper no. 19, page 5, lines 1-2. Nonetheless, the Patent and Trademark Office has never provided any analysis which compares the claims and develops its reasoning as to why the claims of one application would be obvious over the other. As detailed above, the Patent and Trademark Office has erroneously compared sequences disclosed in each specification, but has failed to compare the properly construed claims including all of their recitations.

Merely asserting that two sets of claims are obvious over each other is insufficient to make a *prima facie* case. Merely asserting overlap or a broad-narrow relationship is insufficient to make a *prima facie* case. *In re Michno, supra.* The present rejection fails to explain why the

narrower claims that exclude the signal sequence and provide improved expression are obvious over the claims to nucleic acids that include the signal sequence. The Patent and Trademark Office has failed to make even a bare assertion supporting such alleged obviousness. The Patent and Trademark Office has not provided a sufficient basis to support the conclusion that the claimed invention is an obvious variation of the patented invention.

Respectfully submitted,

November 26, 2003

By: 

Sarah A. Kagan
Reg. No. 32,141

Banner & Witcoff, Ltd.
Customer No. 22907

Enclosures: Declaration of Dr. A. I. Vinik
Xu *et al.*, article
Jarvis *et al.*, article
Berges *et al.*, article